REMARKS

Claims 1-3, 7-10 and 12-20 are pending in the present application. Claims 1-3, 7-10 and 12 are rejected. Claims 13 and 17 are herein amended. New claims 21-24 are added herein. Claims 1-3 and 7-10 are herein cancelled without prejudice. No new matter has been added.

Information Disclosure Statement

With respect to Tanaka et al., the Office Action has once again lined through this reference, while writing "Not in English." The Office Action provides no comment about this in the Office Action. However, Applicants respectfully submit that this is improper.

As explained in MPEP 609.04(III), "each information disclosure statement must further include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information listed that is not in the English language. The concise explanation may be either separate from the specification or part of the specification." The concise explanation of relevance is found in paragraph [0002] of the specification. Therefore, Applicants respectfully request that the Office provide a supplemental SB/08 form in which Tanaka et al. is initialled as having been considered.

Applicants' Response to Claim Rejections under 35 U.S.C. §112

Claims 13-16 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

It is the position of the Office Action that claims 13-16 fail to comply with the enablement requirement. In response to Applicants' previously filed remarks, the Office Action appears to focus on two points.

First, the Office Action appears to question whether pitavastatin is responsible for the improvement of endothelial function. In response, Applicants herein amend the claims to clarify what is meant by "improves endothelial functions." In particular, Applicants herein amend the claims to recite screening for a substance which "improves a vascular disorder which occurs due to the function of a Rac protein." This amendment is supported at least by paragraphs [0008] and [0013] of the specification. Additionally, as explained in Masamura, particularly Figure 1, Rac proteins are very active on the surface of cells or the cytosol of cells. As explained in the caption of Figure 1, "Post translational geranylgeranylation and farnesylation of small G proteins of the Rho/Ras family is an essential prerequisite for their anchoring in the cell member and thus for their activity." Also, Figure 1 shows that statin inhibits the synthesis of mevalonate, and then reduces the number of geranylated proteins. Thus, Masamura shows that Rac is geranylated and thus activated when outside the nucleus. However, Masamura is silent as to regulation of the total number of proteins on the cell surface or in the cytosol. As also explained in the specification, movement of Rac proteins to the nucleus reduces the number of proteins to be geranylated and activated on the cell surface or in the cytosol. This is shown in the difference

between Figure 1 and Figure 2 of the present application. When pitavastatin is added, Rac proteins are moved to the inside of the nucleus before they are geranylgeranylated. Thus, a vascular cell disorder due to the function of the Rac proteins can be improved. In other words, the activation of Rac occurs in the cytosol. The movement of the unactivated Rac protein to the nucleus makes the unactivated Rac protein unavailable for activation. Thus, less activated Rac protein adheres to the cell membrane, causing an improvement of vascular functions.

Furthermore, Applicants herein clarify that the improvement of the disorders is not due to activity of Rac in the nucleus. Rather, since Rac is very active in the cytosol and cell surface, the presence of Rac in the cytosol and cell surface contributes to vascular disorders. The translocation of Rac protein away from the cytosol and cell surface necessarily improves these vascular disorders. This results in a decrease in the number of Rac protein which are activated on the cell surface or in the cytosol. The method of claim 13 screens for a compound which improves the vascular cell disorders by promoting translocation of Rac protein away from the cytosol and cell surface. As discussed in Example 1, pitavastatin is one example of such a compound.

The second issue raised by the Office Action relates to the amount of Rac that must be transferred into the nucleus in order to obtain improvement of endothelial function. Again, the Office Action relies on a hypothetical where nuclear Rac levels are raised by 0.00001%. As stated in the response to the previous Office Action, if transfer of the labeled Rac protein is sufficient to be visualized, a sufficient amount of Rac protein has translocated from the cytosol or cell surface into the nucleus, thereby resulting in an improvement of the vascular cell disorders.

However, in order to clarify this, Applicants herein amend claim 13 to recite a step of "determining that the substance is a substance which improves the vascular cell disorder which occurs due to the function of Rac protein if transfer of the labelled Rac protein into the nucleus of said HUVEC is visually identified." Applicants respectfully submit that this amendment is supported at least by Figures 1-3 and the corresponding text. The translocation of a tiny amount of Rac protein to raise nuclear Rac protein levels by 0.00001% would be insufficient to allow visual identification of translocation. Thus, a compound which gives rise to such a hypothetical, non-visually identifiable 0.00001% increase in nuclear Rac protein levels would not be determined to be a substance which improves a vascular cell disorder. Favorable reconsideration is respectfully requested.

Applicants' Response to Claim Rejections under 35 U.S.C. §103

Claims 17-20 are rejected under 35 U.S.C. §103(a) as being unpatentable over Furuno et al. (J. Immunol 166: 4416-4421, 2001) and Shashidharan et al. (Neuro Report, 10: 1149-1153, 1999).

It is the position of the Office Action that Furuno and Shashidharan each disclose the embodiments as claimed, with the exception of disclosing labeling a Rac protein in HUVEC cells. The Office Action alleges that this would have been obvious. It appears that Furuno and Shashidharan are relied upon in the alternative.

Furuno discloses that nuclear shuttling of mitogen-activate protein (MAP) kinase (Extracellular Signal-Regulated Kinase (ERK) 2) was dynamically controlled by MAP/ERK

Kinase after antigen stimulation in RBL-2H3 cells. Furuno utilized fluorescent protein-tagged ERK2 and MEK to observe nuclear shuttling in RBL-2H3 cells, which are rat basophilic leukemia mast cells. Furuno appears to disclose transport of MAPK (ERK2) into the nucleus due to phosphorylation in response to Ag stimulation. See description of Figure 7.

Shashidharan is directed at nuclear translocation of a GAPDH-GFP fusion protein during apoptosis. It appears that the apoptosis is artificially caused by "an insult." Shashidharan discloses experiments using three cell types: PC12 (rat adrenal pheochromocytoma cells (endocrine tumor)), HEK293 (human kidney cells) and COS-1 (monkey kidney cells).

The Office Action alleges that it would have been obvious to utilize the methodology of Furuno and Shashidharan to monitor the transfer of Rac protein in HUVEC. It appears that the methodology of Furuno and Shashidharan is generally similar to the methodology claimed—labeling a protein of interest with a fluorescent tag and monitoring transport of the protein in response to a substance.

However, in response, Applicants respectfully submit that there is no reason why one having ordinary skill in the art would have modified Furuno or Shashidharan to apply their teachings to Rac protein in HUVEC cells. "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Applicants respectfully submit that the Office Action has provided no articulated reasoning with a rational underpinning as to why it would have been obvious to apply the generic

teaching of monitoring nuclear transport of a protein and apply this to Rac in HUVECs specifically. None of the cited references disclose or suggest the role of Rac. Furthermore, while the cited references discuss rat endocrine tumor cells, human kidney cells, monkey kidney cells and rat leukemia cells, none of the cited references disclose or suggest human umbilical vein endothelial cells, or even endothelial or vascular cells of any kind. In view of this, Applicants respectfully submit that the current rejection of claims 17-19 is merely based on conclusory statements relying entirely on hindsight.

With respect to claim 20, Applicants respectfully clarify that it is only known by one having skill in the art what the general stimulus-response time of HUVECs is. The speed of transfer of Rac protein specifically was not known by one having ordinary skill in the art. Favorable reconsideration is respectfully requested.

New Claims

In addition to the above, Applicants herein add new claims 21-24 reciting a method of screening for a substance which inhibits the function of Rac protein. As discussed above, Rac protein is normally present in the cytosol or on the cell surface and contributes to vascular cell disorders. However, the translocation of Rac away from the cytosol and cell surface inhibits the normal function of the Rac protein. Once the Rac protein has been translocated to the nucleus, it cannot have the function discussed in paragraphs [0008] and [0013]. Thus, Applicants respectfully submit that new claims 21-24 are patentable for similar reasons as claims 13-20, discussed above. Favorable consideration is respectfully requested.

For at least the foregoing reasons, the claimed invention distinguishes over the cited art and defines patentable subject matter. Favorable reconsideration is earnestly solicited.

If the Examiner deems that any further action by applicants would be desirable to place the application in condition for allowance, the Examiner is encouraged to telephone applicants' undersigned attorney.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

WESTERMAN, HATTORI, DANIELS & ADRIAN, LLP

Ryan B. Chirnomas
Attorney for Applicants
Registration No. 56,527
Telephone: (202) 822-1100
Facsimile: (202) 822-1111

RBC/nrp